TREATMENT OF CIRCADIAN RHYTHM DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/378,353, filed Dec. 14, 2016, which is a divisional application of U.S. patent application Ser. No. 14/374,257, filed 24 Jul. 2014, now U.S. Pat. No. 9,549,913, which is the US national phase of PCT/US13/23315, filed 25 Jan. 2013, which claims the benefit of U.S. provisional patent application Nos. 61/590,974, filed 26 Jan. 2012, 61/640,067, filed 30 Apr. 2012, 61/650,455, filed 22 May 2012, 61/650,458, filed 22 May 2012, 61/714,149, filed 15 Oct. 2012, 61/738,985, filed 18 Dec. 2012, 61/738,987, filed 18 Dec. 2012, and 61/755,896, filed 23 Jan. 2013, each of which is hereby incorporated herein as though fully set forth.

FIELD OF THE INVENTION

Embodiments of the invention relate generally to the field of circadian rhythm disorders (CRDs) and, more particularly, to the entrainment of circadian rhythms in persons afflicted with Non-24 Hour Disorder (Non-24).

BACKGROUND OF THE INVENTION

The master body clock controls the timing of many aspects of physiology, behavior and metabolism that show daily rhythms, including the sleep-wake cycles, body temperature, alertness and performance, metabolic rhythms and certain hormones which exhibit circadian variation. Outputs from the suprachiasmatic nucleus (SCN) control many endocrine rhythms including those of melatonin secretion by the pineal gland as well as the control of cortisol secretion via effects on the hypothalamus, the pituitary and the adrenal glands. This master body clock, located in the SCN, spontaneously generates rhythms of approximately 24.5 hours. These non-24-hour rhythms are synchronized each day to the 24-hour day-night cycle by light, the primary environmental time cue which is detected by specialized cells in the retina and transmitted to the SCN via the retino-hypothalamic tract. Inability to detect this light signal, as occurs in most totally blind individuals, leads to the inability of the master body clock to be reset daily and maintain entrainment to a 24-hour day.

Non-24-Hour Disorder

Non-24, also referred to as Non-24-Hour Sleep-Wake Disorder (N24HSWD) or Non-24-Hour Disorder, is an orphan indication affecting approximately 65,000 to 95,000 people in the U.S. and 140,000 in Europe. Non-24 occurs when individuals, primarily blind with no light perception, are unable to synchronize their endogenous circadian pacemaker to the 24-hour light/dark cycle. Without light as a synchronizer, and because the period of the internal clock is typically a little longer than 24 hours, individuals with Non-24 experience their circadian drive to initiate sleep drifting later and later each day. Individuals with Non-24 have abnormal night sleep patterns, accompanied by difficulty staying awake during the day. Non-24 leads to significant impairment, with chronic effects impacting the social and occupational functioning of these individuals.

In addition to problems sleeping at the desired time, individuals with Non-24 experience excessive daytime sleepiness that often results in daytime napping.

The severity of nighttime sleep complaints and/or daytime sleepiness complaints varies depending on where in the cycle the individual's body clock is with respect to their social, work, or sleep schedule. The "free running" of the clock results in approximately a 1-4 month repeating cycle, the circadian cycle, where the circadian drive to initiate sleep continually shifts a little each day (about 15 minutes on average) until the cycle repeats itself. Initially, when the circadian cycle becomes desynchronous with the 24 h day-night cycle, individuals with Non-24 have difficulty initiating sleep. As time progresses, the internal circadian rhythms of these individuals becomes 180 degrees out of synchrony with the 24 h day-night cycle, which gradually makes sleeping at night virtually impossible, and leads to extreme sleepiness during daytime hours.

Eventually, the individual's sleep-wake cycle becomes aligned with the night, and "free-running" individuals are able to sleep well during a conventional or socially acceptable time. However, the alignment between the internal circadian rhythm and the 24-hour day-night cycle is only temporary.

In addition to cyclical nighttime sleep and daytime sleepiness problems, this condition can cause deleterious daily shifts in body temperature and hormone secretion, may cause metabolic disruption and is sometimes associated with depressive symptoms and mood disorders.

It is estimated that 50-75% of totally blind people in the United States (approximately 65,000 to 95,000) have Non-24. This condition can also affect sighted people. However, cases are rarely reported in this population, and the true rate of Non-24 in the general population is not known.

The ultimate treatment goal for individuals with Non-24 is to entrain or synchronize their circadian rhythms into an appropriate phase relationship with the 24-hour day so that they will have increased sleepiness during the night and increased wakefulness during the daytime.

Tasimelteon

Tasimelteon is a circadian regulator which binds specifically to two high affinity melatonin receptors, Mel1a (MT1R) and Mel1b (MT2R). These receptors are found in high density in the suprachiasmatic nucleus of the brain (SCN), which is responsible for synchronizing our sleep/wake cycle. Tasimelteon has been shown to improve sleep parameters in prior clinical studies, which simulated a desynchronization of the circadian clock. Tasimelteon has so far been studied in hundreds of individuals and has shown a good tolerability profile.

SUMMARY OF THE INVENTION

Embodiments of the invention relate to the discovery that tasimelteon can be used to treat a free running circadian rhythm, in patients, including light perception impaired patients, e.g., blind patients, in whom such free running circadian rhythm manifests itself as Non-24.

Embodiments of this invention further relate to the invention of a method for determining a person's circadian rhythm (tau) and to the application of such methodology to the treatment of a free running circadian rhythm.

Embodiments of this invention further relate to the treatment of subjects who present with symptoms of Non-24, specifically, e.g., sleep drifting later each day, abnormal night sleep patterns, and/or difficulty staying awake during the day, leading in many cases to significant impairment, with chronic effects impacting the social and occupational functioning of these individuals, as well as possible negative health effects of chronic misalignment.